REMARKS

Claims 1, 10 and 85-105 are pending in the application and have been rejected.

Claims 91, 92, 97 and 105 have been amended to include identification of the indicated compounds and in claim 97 to correct a spelling error. No other amendments have been made.

Accordingly, claims 1,10 and 85-105 are pending and are presented for reconsideration.

Rejection under 35 USC §103

Claims 1, 10 and 85-105 are rejected under 35 U.S.C. §103(a) as unpatentable over Yamaguchi, *et al.* (*J. Bone and Mineral Research*, v. 13(10) 1998). The Examiner alleges that Yamaguchi teaches that CaR agonists stimulate chemotaxis of cells that have the CaR. While admitting that the reference does not teach administration of an agonist to a subject, the Action takes the position that it would have been obvious to administer an agonist to a subject in order to facilitate migration of any known CaR cell with the reasonable expectation that the cells would migrate to the concentration of the agonists as shown *in vitro* by Yamaguchi. The Action further asserts that "if agonists will effect migration, then antagonists will as well (page 2, paragraph 3 of the Action).

Applicants respectfully disagree. It is Applicants' position that, given the limited cell culture experiments on an osteoblastic clonal mouse cell line, Yamaguchi's finding of a CaR calcium sensing receptor associated with these cells merely supported his suggestion to use this cell line as an *in vitro* model for investigating the role of CaR in osteoblast participation in bone formation. Yamaguchi speculated that this mouse clonal osteoblasic cell line might be an *in vitro* model for studying bone turnover regulation. Yamaguchi did not teach or suggest the method of use for nonCa^{++} calcium-sensing receptor agonists disclosed by Applicants.

The Yamaguchi Reference

In no manner does the Yamaguchi reference even suggest that cells with CaR receptors can be stimulated *in vivo* to migrate, or not to migrate, to designated sites when contacted *in situ* with a non-Ca^{2+} agonist, or antagonist. Applicants can identify neither teaching nor suggestion to enhance CaR receptor expressing cell migration to a specific site in vivo, whether by analogy to Yamaguchi's *in vitro* mouse clonal cell study model, or from any teaching or suggestion taken from a reading of the entire reference.

Applicants have studied the Yamaguchi paper and believe that it teaches use of MC3T3-E1 cells as a potential model for examining the process of osteoblasic development *in vitro* (please refer to Discussion, page 1535, second paragraph). A reading of the entire publication further supports Applicants' understanding of the goal, results and conclusions of the Yamaguchi study as directed to developing an *in vitro* model for investigating bone formation. Whether or not there is application to *in vivo* systems is speculative. The authors state (page 1537, col 2, last paragraph):

> In this study, using MC3T3-E1 cells as a model, we show that osteoplasts, which play an important role in bone remodeling within the skeleton, express both CaR protein and mRNA. Our results suggest that this receptor may be involved in important physiological responses of these cells, such as chemotaxis and proliferation after stimulation by Ca^{2+}. These events are observed at the beginning of the bone formation phase of skeletal remodeling in vivo, suggesting that the CaR could potentially play a key role in the function of bone cells within the bone/marrow microenvironment.

Perhaps more directed to the lack of explicit or implicit teaching of use of agonists (or antagonists) to control cell migration is illustrated in Yamaguchi's statement (page 1537, first paragraph, last sentence):

> Thus, additional studies are needed to document further causal relationships between expression of the CaR, its signal transduction pathways and the control of chemotaxis and cell proliferation by CaR agonists in this osteoblastic cell line.

According, these statements direct one of skill in the art to study Yamaguchi's cell culture model of osteoblast cells in order to determine the responses of these particular cells; however, there is no implicit teaching of how to use knowledge of the effects of high concentration of Ca^{2+}, Gd^{3+} or neomycin sulfate on these cells to enhance chemotactic acitivity *in vivo*.

Looking further in Yamaguchi for teaching or suggestion for Applicants' disclosed methods, Applicants noted that Yamaguchi suggests that other types of cells, including non-specific esterase-positive, monocyte macrophage-like cells present in bone marrow may not have CaR receptors. Yamaguchi used osteoblastic phenotype MC3T3-E1 cells with osteoblast phenotype to "circumvent this problem" (page 1535, Discussion, middle of first paragraph). This again suggested to Applicants that Yamaguchi was trying to understand the role of CaR in cultured mouse osteoblasts and that the objective was to examine "...the process of osteoblastic development in vitro" (page 1535, Discussion, 2nd paragraph, second sentence). They speculated that the MC3T3-E1 cells could be a model for osteoblastic cells and because they expressed CaR for up to 20 days in culture that perhaps *in vivo* cells could express CaR throughout their differentiation, based in part on the possibility that "...a calcium-sensing mechanism is present in these osteoblastic cells and is involved in their migration and proliferation. (page 1536, col 1, first paragraph, line 12-14).

Finally, in an effort to apply any teaching, suggestion or speculation in Yamaguchi to the use of agonists (or antagonists) of CaR to control migration of CaR receptor expressing cells to a specific site *in vivo*, Applicants further examined the Yamaguchi publication. The publication mentions that the role of CaR in the control of cellular proliferation has not been clear until recently, but that CaR has been shown to be involved in stimulation of cell proliferation by CaR agonists. Apparently, others have used fibroblast and 3T3 cells to demonstrate cell proliferation by CaR agonists. In describing other studies, Yamaguchi concluded that they did not contradict his hypothesis that CaR is involved in the proliferation and chemotaxis of MC3T3-E1 cells induced by Ca^{2+} and other CaR agonists. Interestingly, Yamaguchi indicated the need for "additional studies ...to document further causal relationships between expression of the CaR, its signal

transduction pathways and the control of chemotaxis and cell proliferation by CaR agonists in this osteoblastic cell line." Please see col 1, last paragraph bridging over to col 2 on page 1537 through the first paragraph.

Applicants conclude that a fair reading of Yamaguchi indicates to one of skill in the art that there was no suggestion that one could inject a CaR receptor agonist at a specific site *in vivo* with the expectation of enhancing migration of CaR receptor expressing cells to that site. First, there is no indication that what was observed in MC3T3-E1 cells would work *in vivo* to rebuild bone. Importantly, there is no teaching how even an osteoblastic cell *in vivo*, assuming that it expresses CaR receptor protein, would be susceptible in vivo treatment by an agonist to cause site migration.

Finally, Applicants note that there is no reasonable expectation that the effects observed on primitive, early stage osteoblastic cells cultured *in vitro* would be expected to be affected *in vivo* by administering a nonCa^{++} calcium-sensing receptor agonist to cause migration to a specific site.

The lack of predictability in transferring results or findings from cell culture studies to *in vivo* effects has long been admitted by the Patent Office. Generally, only a well-documented animal model showing the same effects as *in vitro* results has been accepted where methods or treatments are claimed for biological systems. In part this arises because there are numerous physiological factors interplaying in biological metabolism. In this case, predictability is speculative, the reference provides no guidance for *in vivo* use, and the "model" showed only that it was difficult to identify a CaR receptor in a primitive cell with no guidance or suggestion to administer an agonist or antagonist to a specific site in order to prevent or induce migration of CaR receptor cells to that site.

Applicants submit that the Yamaguchi reference does not teach or suggest the claimed invention. Removal of the reference as prior art and reconsideration of claim 1, 10 and 85-105 is respectfully requested.

Rejection under 35 U.S.C. §112, Second Paragraph

Claims 91-92 and 105 are rejected as 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The claims are indefinite for failing to clearly represent NPS-2143 and NPS-467, making the claims indefinite. Applicants have amended claims 91, 92 and 105 to include the name of the compounds. The Examiner's attention is drawn to page 41, lines 29-31, of the specification where the source and designation of NPS-R467 and NPS-S467 are specified. The NPS designation is an identifier/trade designation of these compounds available from NPS Pharmaceuticals, Inc. (Salt Lake City, NV) listed on page 41 of the specification.

Applicants have amended claims 91, 92 and 105 to include the chemical names of these compounds. Applicants' specification as filed provides a description of the compound and a source of the compounds so that one skilled in the art can readily obtain and use the exemplary CaR activators. Applicants have additionally provided references that illustrate the chemical name and structures of these compounds, indicating that NPS-S467, NPS-R467 and NPS-2143 are known and available.

Claims 86 has been rejected as improperly depending on cancelled claim 2, and apparently depending on claim 85. Applicants have amended claim 86 to correct this error and request removal of this rejection and reconsideration of the claim.

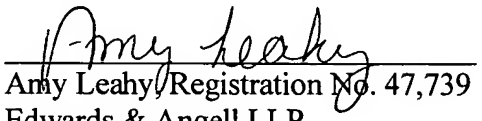
Supplemental Information Disclosure Statement

Applicants submit concurrently herewith a Supplemental Information disclosure Statement for the Examiner's consideration and respectfully request that the cited references be made of record. Copies of the references are included with this document.

Conclusion

Applicants believe that a complete response has been submitted and respectfully submit that this application is now in condition for allowance of claims 61-79. Should any issues remain or should the Examiner believe that a telephone conference with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,



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